New treatment strategies in patients with advanced non-small cell lung cancer with a KRAS mutation

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CHAPTER 2

KRAS Mutated Non-Small Cell Lung Cancer: A Distinct Disease Entity?

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In the era of personalized medicine, cancer research is focused on options for molecularly targeted treatment. In NSCLC, mutations in the gene that encodes the epidermal growth factor receptor (*EGFR*) and the translocation between the genes that encode echinoderm microtubule-associated protein-like-4 and anaplastic lymphoma kinase (*EML4–ALK*) have been identified as predictive markers for particular targeted treatments, with good responses and outcomes in patients who receive these treatments [1,2]. On the other hand, there is no targeted treatment available for patients who have a mutation in *KRAS*, which is the most frequent mutation in patients with NSCLC. The question has been raised as to whether *KRAS*-mutated NSCLC can be considered as a distinct form of lung cancer. In this review, we try to answer this question by discussing the biology of *KRAS* mutation and its clinical behavior in respect of response to chemotherapy and outcome, and provide future perspectives of treatment of patients who have NSCLC with a *KRAS* mutation.

RAS biology

In humans, three *RAS* genes (*HRAS*, *NRAS*, and *KRAS*) have been described that encode four distinct but highly homologous RAS proteins (HRAS, NRAS, *KRAS*4A, and *KRAS*4B) that are approximately 21 kDa each. RAS proteins serve as transducers that couple cell surface receptors such as EGFR to intracellular effector pathways. The RAS proteins cycle between "on" and "off" conformations that are conferred by the binding of guanosine triphosphate (GTP) and guanosine diphosphate (GDP), respectively. Under physiological conditions, the transition between these two states is tightly regulated by guanine nucleotide exchange factors (GEFs), which promote the "on" state by exchange of GDP into GTP, and by GTPase-activating proteins (GAPs), which promote the "off" state by GTP hydrolysis. RAS can harbor transforming properties that are accomplished by gain-of-function mutations. A predominant target of most common somatic mutations in the oncogenic variants of *RAS* gene, such as oncogenic substitutions in residues G12, G13, and Q61, is the diminished inactivation of RAS activity by GAPs. The outcome of these substitutions is the persistence of the GTP-bound "on" state of RAS and, consequently, a constitutively active multitude of RAS-dependent downstream effector pathways. As such, oncogenic RAS functions fuel the tumorigenic process by capturing many of the original, as well as some of the newly established, hallmarks of cancer [3–5].

RAS and NSCLC: a distinct disease entity?

In patients with NSCLC, *KRAS* mutations are the most frequently detected and account for >90% of *RAS* mutations that are found in NSCLC, whereas *HRAS* and *NRAS* mutations are scarce (see the catalogue of somatic mutations in cancer at http://www.sanger.ac.uk/genetics/CGP/cosmic/). As NSCLC may harbor a *KRAS* mutation as a single specific mutated oncogene, this alteration is thought to be the primary genetic "driver" that leads to cancer in these particular cases. It is likely that *KRAS*-mutated NSCLC forms a distinct disease entity having unique tumorigenesis as *KRAS* mutation is found early in the tumorigenesis and exhibits clinicopathological features [6]. *KRAS* mutations are predominantly observed in the adenocarcinoma histotype of NSCLC; approximately 10–30% of lung adenocarcinomas harbor a *KRAS* mutation, mainly (i.e. in >95% of *KRAS*-mutant NSCLC) involving oncogenic substitutions in residues G12 or G13. *KRAS* mutations occur more frequently in smokers than never-smokers [7]. A slight difference in mutation types is noticed. *KRAS* transition mutations (G→A) are more commonly observed in patients who had never smoked cigarettes, whereas transversion mutations (G→T or G→C) are more commonly seen in former/current smokers [8]. The clinical behavior of patients with a *KRAS* mutation will be discussed below.

Preclinical data on *KRAS* and treatment

Treatment of *KRAS*-mutated lung cancer has been found to be quite complex in *in vitro* investigations. Attempted complete knockdown of mutated *KRAS* did not lead to large-scale induction of cell death, and there was an incomplete growth inhibitory effect [9]. It was shown that, although the mitogen-activated protein kinase pathway was significantly downregulated after mutant *KRAS* knockdown, increased levels of phosphorylated signal transducer and activator of transcription-3 (STAT-3) and phosphorylated EGFR, and variable changes in phosphorylated AKT (also known as protein kinase B), occurred. In addition, mutant *KRAS* knockdown appeared to sensitize the NSCLC cell lines to p38 and EGFR inhibitors. This suggests that targeting oncogenic *KRAS* by itself will not be sufficient treatment, but may require the combination of anti-*KRAS* strategies with other targeted drugs.

The effect of the mitogen-activated protein kinase kinase (MEK) inhibitor selumetinib (AZD6244) on the efficacy of docetaxel has been determined in a genetically engineered mouse model of *KRAS*-mutant lung cancers. Concomitant loss of either the gene that encodes tumor protein 53 (*Tp53*) or the gene that encodes liver kinase B1 (*Lkb1*; also known as serine/threonine kinase-11 [*Stk11*]) markedly impaired the response of *KRAS*-mutant cancers to docetaxel monotherapy. However, the addition of selumetinib provided substantial benefit

for mice with lung cancer caused by *KRAS* or *KRAS* and *Tp53* mutations. However, mice with *KRAS* and *Lkb1* mutations had primary resistance to this combination therapy [10]. This suggests that it, in addition to the *KRAS* mutation, is relevant to know any additional underlying mutations.

Using cell-based compound screening coupled with genetic lesion identification, it was shown that *KRAS* mutations confer enhanced heat-shock protein-90 tumor dependency *in vitro* and in mouse model systems [11]. In small interfering RNA studies in lung cancer cell lines, it was found that a RAS pathway signature is a better measure of dependence on RAS than *KRAS* mutation status [12]. A synthetic lethal interaction between *KRAS* and STK-33 has also been shown (i.e. STK-33 activity is required in mutant *KRAS*-driven tumors) [13]. Interestingly, STK-33 functions through inhibition of apoptosis via ribosomal protein S6 kinase β1 (S6K1)-induced inactivation of the death agonist Bcl2 antagonist of cell death (BAD) in mutant *KRAS*-dependent cells. STK-33 expression alone does not appear to be sufficient for tumor initiation and maintenance.

Micro-RNA regulation of KRAS

It has been reported that *KRAS* is inversely regulated by the microRNA (miR) precursor let-7a [14], miR-18a [15], and miR-96 [16]. The oncogenic miR-21 has also been found to regulate *KRAS*-dependent lung tumorigenesis [17]. Recently, it has been shown that miR-622 inhibits the growth of 16HBE-T cells (a malignant transformation of a human bronchial epithelial cell line) by targeting *KRAS* and enhancing the anti-carcinogenic effect of resveratrol [18]. Rational therapies that target the RAS pathways could potentially inhibit tumor growth, survival, and spread.

The RAS pathway is activated in a greater number of NSCLC cell lines than those that have been found to have *KRAS* mutations. Analysis of the mutations in these *KRAS* wild-type cell lines might expand the population of RAS-pathway-activated tumors. Preclinical studies have also demonstrated that integrated genomic and proteomic analyses can be used to identify targeted treatments for RAS-pathway-activated tumors. Although these preclinical discovered targeted therapies look promising, the therapeutic effect in the clinical setting remains to be determined.

KRAS as a prognostic biomarker

In 1990, *KRAS* mutational status was identified by Slebos et al. as a negative prognostic marker in patients with early-stage NSCLC after complete resection [19]. In this study, 19 of 69 patients (27.5%) had a *KRAS* mutation. The rates of disease-free survival and overall survival (OS) were significantly worse in patients with a *KRAS* mutation (p=0.038 and p=0.002, respectively). Since then, a variety of studies have prospectively investigated the prognostic role of *KRAS* mutations in patients with NSCLC (**Table 1**). In a randomized clinical trial, 184 patients with resected stage II and IIIA NSCLC were assigned to adjuvant radiotherapy with or without chemotherapy [20]. Forty-four (23.9%) of these patients had a *KRAS* mutation. The median length of OS in the patients with a *KRAS* mutation was 30 months (95% confidence interval [CI] 34–64 months) compared with 42 months (95% CI 34–64 months) in patients with wild-type *KRAS* (wt-*KRAS*; p=0.38). No differences in progression-

Table 1. Prognostic value of *KRAS* mutational status in patients with NSCLC

Author [ref]	Stage	Histology	Number of patients	*KRAS* mutant tumors (%)	Prognostic significance
Slebos et al. 1990 [19]	I-IIIa	Adenocarcinoma	69	27.5	Negative
Sugio et al. 1992 [50]	I-IV	Adenocarcinoma	115	15.7	None
Silini et al. 1994 [51]	I-IV	Adenocarcinoma	109	30.3	None
Rosell et al. 1993 [52]	I-IV	All	275	20.7	Negative
Fukuyama et al. 1997 [53]	I-IV	All	162	6.9	Negative
Siegfried et al. 1997 [25]	I-IV	Adenocarcinoma	181	31.5	None
Schiller et al. 2001 [20]	II-IIIa	All	184	24	None
Broermann et al. 2002 [54]	III	All	28	46	None
Sasaki et al. 2007 [21]	I-IV	All	190	11.1	Negative
Scoccianti et al. 2012 [22]	I-III	All	249	18.5	None

free survival (PFS) were observed. In patients with N1 disease, those with wt-*KRAS* had a significantly better median length of OS compared with patients who had *KRAS* mutations (45.2 vs. 23.6 months; p=0.02) [20].

In a Japanese study, tissue from 195 patients with resected NSCLC was analyzed for mutational status. Twenty-one of 190 patients (11.1%) had a *KRAS* mutation. More advanced-stage patients (stage II–IV, 13 of 73 patients) had *KRAS* mutations than early-stage patients (eight of 117 patients; p=0.019). Patients with a *KRAS* mutation had a significantly worse survival rate than those with wt-*KRAS* (p=0.001). Despite its higher prevalence in patients with a more advanced stage of NSCLC, *KRAS* mutation remained an independent prognostic factor (p=0.021) [21].

The most recent study recruited patients with surgically resected early-stage lung cancer. Overall, 46 of 249 (18.5%) patients had a *KRAS* mutation. *KRAS* mutational status was not associated with prognosis (hazard ratio [HR] 1.3, 95% CI 0.82–2.06; p=0.26). However, patients with concurrent *TP53* and *KRAS* mutations had a poorer prognosis (HR 3.26, 95% CI 1.07–9.90; p=0.038), although few patients had both mutations [22].

In a meta-analysis of 53 studies, patients with NSCLC with a *KRAS* mutation had a worse survival than those with NSCLC without a *KRAS* mutation (HR 1.40, 95% CI 1.18–1.65) [23]. In those with adenocarcinoma, the HR was 1.50 (95% CI 1.26–1.80). Unfortunately, there was no correction for performance status and stage of disease as prognostic confounders, which therefore precludes a definite conclusion. One study described differences in survival between patients with different types of *KRAS* mutation [24]. In this study, lung cancer tumor tissue from 173 patients was screened after lung resection, and 43 patients were found to have a *KRAS* mutation (24.9%). *KRAS* mutational status overall was not related to poor survival (p=0.96). However, when the investigators looked at different types of *KRAS* mutation there was a near-significant trend for shorter survival in the group with G12V and G12R mutations (n=13; p=0.07) compared with the wild-type group. Patients with G12D (n=9) had a trend towards better survival than the wild-type patients (p=0.06). Because of the small numbers, a larger retrospective study with 181 patients with resected lung adenocarcinoma was performed by the same investigators [25]. In 57 patients (31.5%) a *KRAS* mutation was detected. Again, in this larger cohort of patients, *KRAS* mutational status was not significantly associated with survival (p=0.64). Breakdown by types of *KRAS* mutation revealed G12V to display a better survival than other types, contrary to the previous study.

In summary, the prognostic role of *KRAS* mutation is not clear because of the conflicting outcomes obtained in the studies discussed. These studies were difficult to compare because of selection bias and variation in disease stage and histology. Whether some types of *KRAS* mutation have greater prognostic value than others could not be determined because of conflicting data.

Table 2. *KRAS* mutational status and response to chemotherapy in patients with NSCLC

Author [ref]	Stage	Chemotherapy	Histology	Number of patients	*KRAS mut* (%)	Response rate		Median OS (months)	
						KRAS mut	*KRAS wt*	*KRAS mut*	*KRAS wt*
Tsao et al. 2007[26]	Ib-II	Cisplatin/ vinorelbine (adjuvant)	All	450	26	NA	NA	74	NR
Rodenhuis et al. 1997[27]	III-IV	Mesna, ifosfamide, carboplatin and etoposide	Adeno-carcinoma	62	26	19%	26%	8	9 (p=0.22)
Eberhard et al 2005[55]	IIIb-IV	Carboplatin/ paclitaxel	All	264	21	23%	26%	13.5	11.3 (NS)
Kalikaki et al. 2010[28]	IV	Several	All	133	23	25%	26.5%	14.5	18.5 (p=0.52)

Abbreviations: mut: mutation; wt: wild type; NA: not applicable; NR: not registered; NS: not significant; OS: overall survival

Clinical value of *KRAS* mutational status and prediction of standard chemotherapy response

The results of some key studies of *KRAS* mutational status and response to chemotherapy in NSCLC are summarized in **Table 2**. In a randomized Phase III study by Tsao et al., a total of 482 patients with NSCLC were recruited to determine the effect of adjuvant vinorelbine plus cisplatin versus observation [26]. In 117 of 450 patients (26.0%) a *RAS* mutation was found, equally divided amongst both groups. The median length of survival in patients with wt-*RAS* was reduced in the observation arm compared with that in the patients who were treated with chemotherapy (HR 0.69, 95% CI 0.49–0.98; p=0.03). *RAS*-mutated patients appeared to gain no benefit in terms of survival from adjuvant chemotherapy (HR 0.95, 95% CI 0.53–1.71; p=0.87). Although wt-*RAS* patients appeared to derive greater benefit from adjuvant

chemotherapy than patients with mutant *RAS*, this was not statistically significant (p=0.29) [26].

In a prospective trial to determine if *KRAS* mutations should routinely be determined in patients with lung adenocarcinoma, 62 patients with inoperable stage III or IV NSCLC were treated with mesna, ifosfamide, carboplatin, and etoposide [27]. For this study, biopsy material had to be assessable to determine *KRAS* mutational status. Sixteen patients (25.8%) had a *KRAS* mutation. In 19% of patients with a *KRAS* mutation, there was a response to treatment. In the group with wt-*KRAS,* 26% had a response to chemotherapy. This difference in response rate was not significant (p=0.49). The median length of PFS was 5 months and 4 months (p=0.29) in patients with wt-*KRAS* and *KRAS* mutations, respectively, with corresponding median OS times of 9 months and 8 months (p=0.22). This well-designed study suggests that *KRAS* mutational status has no clinical significance in chemotherapy treatment of patients with an advanced lung adenocarcinoma.

In the most recent study, 162 patients with stage IV NSCLC were treated with first-line chemotherapy [28]. Thirty of 133 patients (22.6%) had a *KRAS* mutation. A total of 96 patients (59.2%) received platinum-based chemotherapy. Evaluation of the whole study population found no difference in response to chemotherapy between patients with mutated *KRAS* and those with wt-*KRAS* (25.0% vs. 26.5%; p=0.87). In addition, no difference was found in patients who were treated with platinum-based chemotherapy (29.2% vs. 30.2%, respectively; p=0.95). Time to progression (TTP) was 4.2 months versus 4.7 months (p=0.42), and the length of OS was 14.5 months versus 18.5 months (p=0.52).

Only a few studies have investigated the predictive value of *KRAS* mutations in patients with NSCLC who were treated with chemotherapy alone. Considering these data, *KRAS* mutation seems to not be of predictive value in treatment of NSCLC with (platinum-based) chemotherapy.

Predictive value of *KRAS* mutational status in EGFR-TKI treatment

The results of key studies of *KRAS* mutational status and response to EGFR tyrosine kinase inhibitors (TKIs) are summarized in **Table 3**. In a retrospective study on the predictive value of *EGFR* mutation and *KRAS* mutation, patients with NSCLC who were treated with gefitinib or erlotinib were studied [29]. A *KRAS* mutation was identified in 16 of 70 patients (22.8%). The presence of a *KRAS* mutation was significantly associated with a lack of response to TKI treatment. All 16 patients with *KRAS* mutations experienced progressive disease as the best response to treatment with EGFR-TKIs, whereas seven of the 54 patients with wt-*KRAS* had a

Table 3. *KRAS* mutational status and response to EGFR tyrosine kinase inhibitors in NSCLC patients

Study	Therapy	Nr. Of patients	*KRAS* mut (%)	Response		
				KRAS mut	*KRAS* wt	*KRAS* wt and EGFR wt
Pao et al. 2005[56]	Gefitinib/erlotinib	59	15	0/9	17/51 p=0.02	5/22 p=0.29
Han et al 2006[57]	Gefitinib	69	16	0/9	16/60 p=0.10	8/45
Giaccone et al 2006[58]	Erlotinib	29	35	0/10	4/15 NC	NA
Massarelli et al. 2007 [29]	Gefitinib/erlotinib	70	23	0/16	7/54 p=0.04	2/47
Miller et al. 2008[59]	Erlotinib	101	18	0/18	6/20 p=<0.01	5/44
Zhu et al. 2008[60]	Erlotinib	118	17	1/20	10/98 p=0,69	6/83
Marchetti et al. 2009[30]	Gefitinib/erlotinib	83	36	0/30	9/53 p=0.004	2/33
Douillard et al. 2010 [61]	Gefitinib	114	18	0/20	9/94 NS	NA
Tiseo et al. 2010 [62]	Gefitinib	63	11	0/7	14/56 P=0.33	5/45
Schneider et al. 2008 [63]	Erlotinib	114	15	0/11	7/78 P=0.59	5/74
Ludovini et al. 2011 [64]	Gefitinib/erlotinib	162	7	0/11	54/151 P=0.03	25/109
Hirsch et al. 2007 [65]	Gefitinib	138	26	3/36	19/102 P= 0.24	8/60
Felip et al. 2008 [66]	Erlotinib	39	18	0/7	3/39 NC	1/34
Zucali et al. 2008 [67]	Gefitinib	49	31	0/15	3/34 P= 0.54	0/30
Jackman et al. 2009 [68]	Gefinitib/erlotinib	171	24	0/41	36/130	4/83 P <0.001

Abbreviations: wt: wild type, mut: mutation, NS: not significant, NC: not calculated

complete response to treatment(p=0.04). Patients with a *KRAS* mutation had a shorter TTP (1.7 months vs. 2.9 months; p=0.0025); they also had a shorter median length of OS, although this was not significant (5.0 months vs. 9.4 months; p=0.62). Another retrospective study evaluated treatment with an EGFR-TKI in 83 patients with lung adenocarcinoma [30]. This study used two methods to determine *KRAS* mutational status: direct sequencing and mutant-enriched (ME) sequencing. ME sequencing was found to be the most sensitive method in this study. Thirty of the 83 patients (36.1%) had a *KRAS* mutational status as detected by ME sequencing compared with 16 patients who had mutations detected by direct sequencing. None of these 30 patients responded to erlotinib or gefitinib compared with nine of 53 patients with wt-*KRAS* (p=0.004). In a multivariate regression analysis, *KRAS* mutation was found to be an independent predictor of poor disease control (p=0.019). Patients with a *KRAS* mutation also had significantly poorer PFS (HR 1.87, 95% CI 1.08–3.24; p=0.02) and OS (HR 2.29, 95% CI 1.23–4.25; p=0.01) outcomes.

The most recent study prospectively evaluated the role of biomarkers in predicting clinical outcomes with erlotinib treatment, using data from the SATURN (Sequential Tarceva in Unresectable NSCLC) trial [31]. This was a Phase III, placebo-controlled trial evaluating maintenance treatment with erlotinib in patients with non-progressive disease following first-line platinum-doublet chemotherapy. Ninety of 493 patients (18.3%) had a *KRAS* mutation. *KRAS* mutational status in the placebo arm was a significant negative prognostic factor for PFS (HR 1.50, 95% CI 1.06–2.12; p=0.020), but not for OS (HR 1.31, 95% CI 0.90–1.90; p=0.152). Erlotinib provided no PFS benefit in patients with a *KRAS* mutation (HR 0.77, 95% CI 0.50–1.19; p=0.225). The interaction between treatment and *KRAS* mutational status was not significant (p=0.95), indicating that erlotinib had no differential effect on PFS [31].
A meta-analysis of 22 studies has described the relationship between *KRAS* mutation and resistance to EGFR-TKI treatment. *KRAS* mutations were found in 231 of 1470 patients (15.7%). The objective response rates for patients with a *KRAS* mutation and those with wt-*KRAS* were 3% and 26%, respectively (relative risk 0.29, 95% CI 0.18–0.47; p=0.01) [32]. This meta-analysis supports the association between *KRAS* mutation and a lack of response to EGFR-TKI therapy.

In summary, *KRAS* mutation seems to be a predictor for refractory effect to EGFR-TKIs. The studies discussed in this section show that patients with *KRAS* mutations did not respond to erlotinib or gefitinib. In **Table 3**, the rate of response in patients with both wt-*KRAS* and wt-

EGFR is also listed. The findings suggest that this group of patients is not significantly different from patients with a *KRAS* mutation.

Potential use of RAS or downstream pathway members as target(s) for inhibitory treatment

Several clinical studies report results on targeted treatment in *KRAS*-mutated NSCLC. In the BATTLE (Biomarker-Integrated Approaches of Targeted Therapy for Lung Cancer Elimination) trial, 158 patients with advanced NSCLC who had failed previous treatment were randomized to treatment with erlotinib, vandetanib, erlotinib plus bexarotene, or sorafenib according to mutational status [33]. Patients with a *KRAS* mutation receiving sorafenib had a disease control rate of 79% (11 of 14 patients). Sorafenib had the highest efficacy in patients with *KRAS*-mutated disease. Other treatments were less successful in patients with a *KRAS* mutation. This suggests that patients with a *KRAS* mutation may benefit from treatment with sorafenib, although the trial result was not significant. The rationale for this success of sorafenib in patients with a *KRAS* mutation is that sorafenib inhibits, amongst other molecules, CRAF and BRAF, which are downstream effectors of RAS. Another study also showed activity of sorafenib in patients who had NSCLC with a *KRAS* mutation, but the number of *KRAS*-mutated patients was small [34]. Recently, our group performed a Phase II study of sorafenib in 57 patients with a *KRAS* mutation. Sorafenib was found to be active in these patients, with a disease control rate at 6 weeks of 52.6%, but poor outcomes [35]. To increase the effectiveness of treatments in these patients, combination therapy might be a possibility.

In patients with leukemia, two studies have described a paradoxical activation of the RAF/MEK/extracellular-regulated kinase (RAF/MEK/ERK) pathway with weak RAF inhibitors (e.g. imatinib and dasatinib). These studies conclude that when RAS is activated, the RAF/MEK/ERK pathway is paradoxically hyperactivated when RAF is inhibited [36,37]. It is not clear if these results are also applicable in patients with lung cancer, but this finding could have major implications for the long-term treatment of (lung) cancer patients with a *KRAS* mutation.

Two promising agents for the treatment of *KRAS*-mutated NSCLC are selumetinib (a MEK inhibitor) and ridaforolimus (a mammalian target of rapamycin [mTOR] inhibitor). In a double-blind, Phase II study, 87 patients who had NSCLC with a *KRAS* mutation were randomized to receive docetaxel or docetaxel and selumetinib. The primary endpoint (OS) was not reached, but the response rate and PFS rate were significantly improved for patients who were treated with selumetinib and docetaxel compared with docetaxel alone [38]. A

Phase II study has reported a prolonged PFS in patients with *KRAS*-mutant NSCLC who had stable disease after 8 weeks of treatment with ridaforolimus and continued treatment with ridaforolimus compared with those who received placebo [39]. These studies explore novel treatment possibilities for patients who have NSCLC with a *KRAS* mutation.

Concurrent inhibition of the RAS/RAF pathway and the phosphoinositide 3-kinase (PI3K)/mTOR pathway may be synergistic. Phase I studies in patients with renal cell and hepatocellular cancer have shown that the combination of everolimus and sorafenib was active and tolerable [40,41]. Phase I studies with everolimus and sorafenib are ongoing in patients with lung cancer [42]. Other Phase studies are also focusing on combination treatment with NVP-BEZ235 (a dual PI3K/mTOR inhibitor) and an inhibitor of the RAF/MEK/ERK pathway. Future clinical studies should evaluate whether concurrent inhibition of the PI3K pathway and RAS/RAF pathway is beneficial for patients who have NSCLC with a *KRAS* mutation. It can be expected that combination therapy will enhance toxicity.

Recently, there has been renewed attention towards determining the effects of different types of *KRAS* mutation. There are suggestions that the different kinds of *KRAS* mutations react differently to treatment [43]. G12C and G12V mutations have been found to be more aggressive than other type of *KRAS* mutations [44]. In addition, it has been reported that patients with *KRAS* mutations in codon 13 have a poorer PFS and OS compared with those who have a codon 12 *KRAS* mutation [45]. In patients with colorectal cancer it appears that those with a G13D mutation have a poorer response to treatment than patients with other *KRAS* mutations [46,47]. This raises the interesting question of whether the types of *KRAS* mutation in patients with lung cancer have different contributions to tumorigenesis. It is difficult to answer this question because no studies have been published that have tried to correlate types of *KRAS* mutation and other known driver mutations [48].

Thus, *KRAS* mutations have the potential to be successfully targeted downstream. Combination therapy has to be the focus of future research, although toxicity may be a problem. Emerging data suggest that the types of *KRAS* mutation are not all alike. Future clinical trials in patients with a *KRAS* mutation should analyze the types of *KRAS* mutation because data on the effect of types of *KRAS* mutation on response to treatment and survival are presently scarce.

Conclusion

To answer the question of whether or not *KRAS*-mutated NSCLC forms a distinct disease entity, as posed in the introduction, several factors have to be taken into consideration. In terms of outcome and response, the answer seems to be "no". It appears that *KRAS* mutation is not a marker for prognosis, nor does it predict response to chemotherapy. In spite of the latter finding, *KRAS* mutation is a predictor of lack of benefit from treatment with an EGFR-TKI. However, Canadian consensus recommendations, for example, state that testing of *KRAS* mutation is not required when selecting treatment [49].

With respect to whether or not RAS or downstream pathway components might be a target(s) for inhibitory treatment, the answer seems to be "yes". Such targeted treatment in patients with a *KRAS* mutation has promise. The RAS/RAF signaling pathway is a promising therapeutic target given its central role in regulation of cell proliferation. Recent insights show that concurrent inhibition of both the RAS/RAF and PI3K/mTOR pathway will be more successful than single-target inhibition. There are many treatment options that have demonstrated a good outlook for patients with a *KRAS* mutation in early phase clinical trials.

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